

## INVITED REVIEW

# The transport function of the human lymphatic system—A systematic review

Lene Thorup<sup>1,2</sup>  | Anders Hjortdal<sup>3</sup> | Donna B. Boedtkjer<sup>4</sup> | Morten B. Thomsen<sup>5</sup> | Vibeke Hjortdal<sup>1,2</sup> 

<sup>1</sup>Department of Cardiothoracic Surgery, Copenhagen University Hospital, Copenhagen, Denmark

<sup>2</sup>Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

<sup>3</sup>Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

<sup>4</sup>Department of Biomedicine, Faculty of Health, Aarhus University, Aarhus, Denmark

<sup>5</sup>Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark

## Correspondence

Lene Thorup, Department of Cardiothoracic Surgery, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen, Denmark.  
Email: [lene.thorup.01@regionh.dk](mailto:lene.thorup.01@regionh.dk)

## Funding information

Bent Thorbergs Foundation (Private foundation); The Novo Nordisk Foundation, Grant/Award Number: NFF17SA0030576

## Abstract

Physiological properties and function of the lymphatic system is still somewhat of a mystery. We report the current knowledge about human lymphatic vessel contractility and capability of adaptation. A literature search in PubMed identified studies published January 2000–September 2022. Inclusion criteria were studies investigating parameters related to contraction frequency, fluid velocity, and lymphatic pressure in vivo and ex vivo in human lymphatic vessels. The search returned 2885 papers of which 28 met the inclusion criteria. In vivo vessels revealed baseline contraction frequencies between  $0.2 \pm 0.2$  and  $1.8 \pm 0.1 \text{ min}^{-1}$ , velocities between  $0.008 \pm 0.002$  and  $2.3 \pm 0.3 \text{ cm/s}$ , and pressures between 4.5 (range 0.5–9.2) and  $60.3 \pm 2.8 \text{ mm Hg}$ . Gravitational forces, hyperthermia, and treatment with nifedipine caused increases in contraction frequency. Ex vivo lymphatic vessels displayed contraction frequencies between  $1.2 \pm 0.1$  and  $5.5 \pm 1.2 \text{ min}^{-1}$ . Exposure to agents affecting cation and anion channels, adrenoceptors, HCN channels, and changes in diameter-tension properties all resulted in changes in functional parameters as known from the blood vascular system. We find that the lymphatic system is dynamic and adaptable. Different investigative methods yields alternating results. Systematic approaches, consensus on investigative methods, and larger studies are needed to fully understand lymphatic transport and apply this in a clinical context.

## KEYWORDS

lymphatic function, lymphatic system, lymphedema, physiology, thoracic duct

## 1 | INTRODUCTION

Since the discovery of human lymphatic tissue dating back to Ancient Greece, our understanding of the lymphatic system has developed significantly (Suy et al., 2016).

Arranged throughout the body much like the venous network, the lymphatic vascular system serves a

multitude of functions. Aside from being an essential part of the immune response (Oliver & Alitalo, 2005) it also plays a central role in the uptake of dietary fat. Upon absorption across the intestinal mucosa, fatty acids and monoglycerides are joined together with proteins, cholesterol, and other constituents to form chylomicrons, which are then transported to the bloodstream by the lymphatic

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2023 The Authors. *Physiological Reports* published by Wiley Periodicals LLC on behalf of The Physiological Society and the American Physiological Society.

vasculature in the form of chyle (Breslin et al., 2018; Cifarelli & Eichmann, 2019; Hokkanen et al., 2019).

Additionally, lymphatic vessels play an important role in transporting interstitial fluid and extravasated proteins back to the systemic circulation thereby maintaining fluid homeostasis (Telinius & Hjortdal, 2019). According to the Starling Principle, tissue fluid homeostasis is determined by the hydrostatic and osmotic pressures in the interstitium and capillaries (Levick, 2004; Woodcock & Michel, 2021). A recent revision of this concept has proposed that due to the endothelial glycocalyx acting as a semipermeable layer between the capillary lumen and the endothelium under steady-state conditions, the reabsorption into the venous system may not be the major route for returning interstitial fluid to the circulation. As a space is created between the glycocalyx and the endothelium, into which proteins are filtered, it is across this luminal barrier that the osmotic force primarily exerts its effect. However, because of consistent fluid flux from the capillary to the interstitium, these proteins are continuously moved out of this space and into the interstitium, where they do not have any osmotic effect: this essentially obliterates the interstitial osmotic force during steady-state conditions, which means filtration is driven by the hydrostatic pressure. Since the pressure in the interstitial space will always be negative in steady state, filtration will dominate with practically no absorption into the capillaries (Michel et al., 2020).

Consequently, 8–12 liters of fluid returns to the systemic circulation via the lymphatic vasculature in the course of a day (Scallan et al., 2016). This transport is organized through a vast system of peripheral lymphatic capillaries coalescing into increasingly larger collecting vessels until terminating into the central venous system at the subclavian level (Brotons et al., 2012). The transport is unidirectional, promoted by intraluminal valves and myogenic smooth muscle cells in the lymphatic vessel wall (Adamczyk et al., 2016; Alitalo, 2011), possibly with influence from pacemaker-like cells located in the lymphatic vessels (Briggs Boedtkjer et al., 2013). Additionally, some of the lymphatic fluid is returned to the blood via lymphatic-venous anastomoses in lymph nodes. Failure of this system can manifest itself in many forms, from peripheral lymphedema to the centralized organ dysfunction as seen in plastic bronchitis, chylothorax, and protein-losing enteropathy (Kelly et al., 2020).

Despite this advanced understanding of key processes in the lymphatic system including the origin and destination of interstitial fluid, unanswered questions about the steps along its way remain.

During the last decades, it has become increasingly clear that modifying lymphatic flow is an unmet medical

need. The aim of this review is to systematically describe the quantifiable physiological parameters (contraction frequency, velocity, and pressure) of human lymphatic flow function by compiling the knowledge as it is reported in the recent literature.

## 2 | METHODS

This review was conducted according to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). A Prisma checklist is available in Appendix S1.

### 2.1 | Eligibility criteria

Studies reporting on the physiologic properties of lymphatic vessel function and lymphatic flow parameters in humans or human lymphatic vessels were eligible for inclusion. Physiological parameters were defined as a measurable unit reporting on either: (1) frequency as number of contractions in a given time, (2) velocity reported with quantitative measurements of a distance in a given time, (3) pressure or tension measured in any relevant unit. Only studies reporting original data in humans and from human tissue were considered.

The following exclusion criteria were used for *in vivo* studies: (1) data presented without measurable parameters, for example, transit time without transit distance, (2) reporting of data from diseased lymphatic vessels without the inclusion of a control group, either healthy controls or acting as own control in a nonaffected limb, (3) not written in English, (4) nonhuman participants, (5) the article was a review, letter, comment, meta-analysis, or conference abstract, (6) articles published before January 1st, 2000. The same exclusion criteria were used for *ex vivo* studies except from the inclusion of lymphatic vessels harvested from patients.

### 2.2 | Search strategy

A systematic search was carried out in PubMed, using a combination of both MeSH terms and Title/Abstract related to “lymphatic function”, “physiology”, and “pharmacology”. A detailed search string is available in the Appendix S1. The search was carried out in April 2022 and updated in September 2022. Reference lists of included studies were screened to obtain additional literature. A structured reference review of the included studies was conducted to confirm all relevant articles were included.

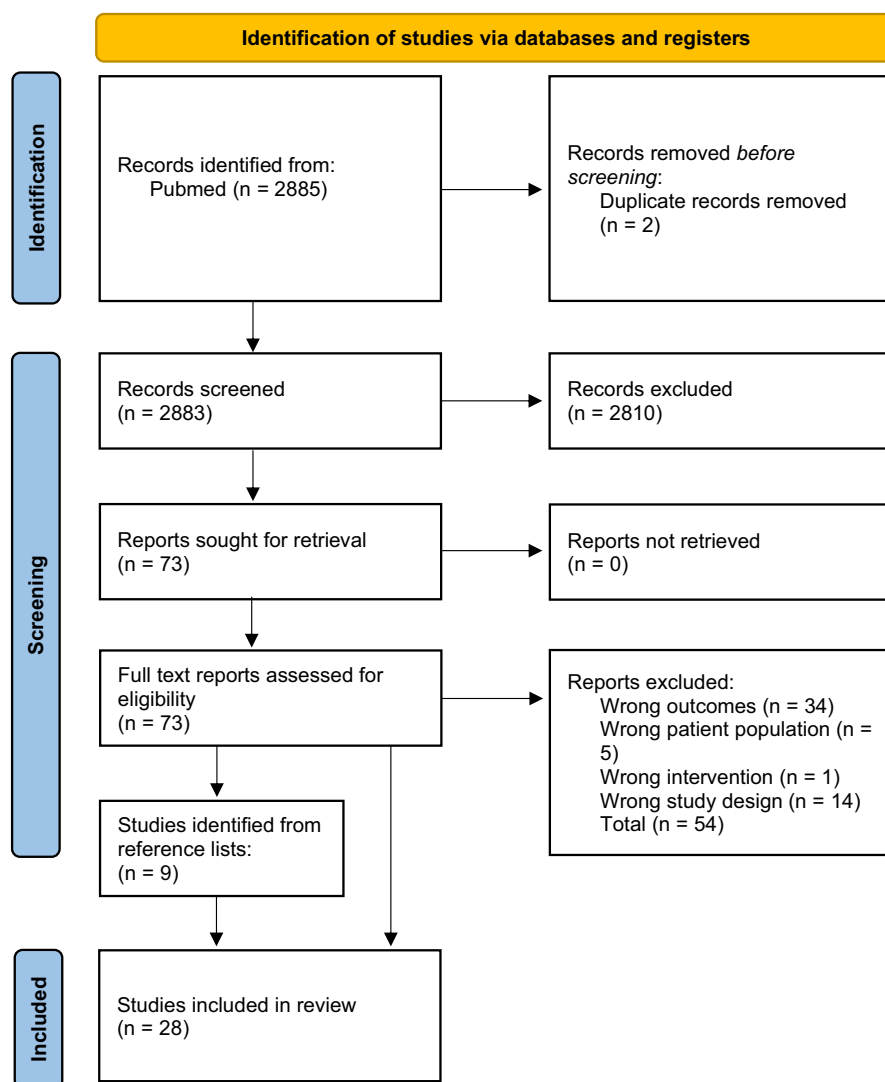
## 2.3 | Study selection and data extraction process

This review utilized Covidence.org (Covidence systematic review software (2022) for reference management. After the removal of duplicates, authors AH, VH, and LT independently screened the articles by title and abstract for relevance. Eligible studies were then independently assessed by the same three authors, referring to the previously defined inclusion and exclusion criteria. At each step, at least two reviewers had to agree on either exclusion or inclusion. Any disagreement was solved by consensus in the reviewer group.

Studies were sorted into either in vivo or ex vivo designs. Data extracted from in vivo studies included baseline characteristics: author, year of publication, number of participants, age, comorbidities, functional parameters (lymphatic flow velocity and/or pressure; frequency of vessel contraction), study intervention (if any), control

group (if any), and postintervention functional parameters. Ex vivo data included the same basic information along with contraction frequency and two measures of tension properties: passive/baseline and active. Passive tension is the tension measured in the isolated vessel at its relaxed, baseline level. Active tension is the tension measured at spontaneous or stimulated contraction minus the baseline tension.

Figures were created using GraphPad Prism (version 8.0.2 for Windows, GraphPad Software, San Diego, California USA), displaying the distribution of functional parameters in in vivo studies, reported with mean and standard deviation when available. A comparison of the effect of interventions was also plotted. Units for each parameter were defined as (1) frequency: vessel contractions per minute (2) fluid pressure: mm Hg, (3) fluid velocity: centimeters per second. Any parameters stated in other units in the original articles were converted to these predefined units for the plots and tables.



**FIGURE 1** PRISMA 2020 flow diagram of inclusion of papers for systematic review.

TABLE 1 Summary of in vivo functional properties.

In Vivo Summary									
Reference	N	Age, Years	Control group	Morbidity	Method	Limb	Baseline		
							Control/healthy		
							Frequency (contractions/min)	Pressure (mm Hg)	Velocity (cm/s)
Amann-Vesti (2003) Lymphatic Research and Biology	22	15–62	Healthy	Fabry Disease	Lymphatic capillary puncture	Leg		6.9 (1.5–13)	
Belgrado (2016) Lymphatic Research and Biology	30	43 ± 14	NA	Healthy	NIRF (ICG)	Arm			
Bell (2020) Arthritis Rheumatol.	13	49 ± 14.3	Healthy	Rheumatoid arthritis	NIRF (ICG)	Hand	0.51 ± 0.35		
Gray (2016) Medical Engineering and Physics	10	24–61	NA	NA	NIRF (ICG)	Arm			Median 0.8 (0.4–2) <sup>a</sup>
Groenlund (2017) Lymphatic Research and Biology	10	20–30	NA	Healthy	NIRF (ICG)	Leg	0.59 ± 0.13	56 ± 9–57 ± 9	1.51 ± 0.24
Holm-Weber (2022) Physiological Reports	17	Male: 29 ± 2.7 Female: 27 ± 2.6	NA	Healthy	NIRF (ICG)	Leg	0.5 ± 0.2		1.50 ± 0.4
Kelly (2020) Lymphatic Research and Biology	10	25.7 ± 1.3	NA	Healthy	NIRF (ICG)	Arm	0.9 ± 0.4	59 ± 12	1.1 ± 0.3
Lopera (2017) Lymphatic Research and Biology	9	36 (22–58)	NA	Healthy	NIRF (ICG)	Arm	Forearm: 0.8 <sup>a</sup> Elbow: 1.4 <sup>a</sup>		Forearm: 0.76 <sup>a</sup> Elbow: 1.08 <sup>a</sup>
Modi (2007) J Physiol	39	Uncuffed: 52 ± 10 Cuffed: 54 ± 6 BCRL: 60 ± 8	Healthy	BCRL	99mTc-HIG dermal injection	Arm		39 ± 14	Uncuffed: 0.15 ± 0.1 <sup>a</sup> Cuffed: 0.13 ± 0.18 <sup>a</sup>
Mohanakumar (2019) Circ Cardiovasc Imaging	20	Fontan: 24 ± 7 Control: 26 ± 2	Healthy	Fontan circulation	NIRF (ICG)	Leg	0.5 ± 0.1	60.3 ± 2.8	1.9 ± 0.2 <sup>a</sup>
Mohanakumar (2020) Lymphatic Research and Biology	16	56.5 ± 6.9	NA	Healthy	NIRF (ICG)	Leg	0.4 ± 0.3	54.7 ± 9.4	1.5 ± 0.7
Mohanakumar (2021) Physiological Reports	48	Fontan: 27 ± 7 Control: 27 ± 9	Healthy	Fontan Circulation	NIRF (ICG)	Leg	0.3 ± 0.2	57.2 ± 8.4	1.6 ± 0.5 <sup>a</sup>
Rane (2013) Radiology	12	31–64	Healthy	Mastectomy w/ LE	Spin Label Measurement	Arm			0.01 ± 0.002 <sup>a</sup>
Rasmussen (2010) Translational Oncology	44	Healthy: 38.2 ± 11 Diseased: 49.7 ± 17.6	Healthy and Own Control	LE	NIRF (ICG)	Arm and Leg	H-Arm: 1.3 ± 1.2 OC-Arm: 1.2 ± 1.0 H-Leg: 0.4 ± 0.3 OC-Leg: 0.3 ± 0.2		H-Arm: 0.8 ± 0.4 OC-Arm: 0.8 ± 0.4 H-Leg: 0.9 ± 0.7 OC-Leg: 0.8 ± 0.5
Rasmussen (2021) J Vasc Surg Venous Lymphat Disord	20	CVI: 53.5 (38–70) Control: 43.0 (30–58)	Healthy	Chronic venous insufficiency	NIRF (ICG)	Leg	0.9 ± 0.4		
Rasmussen (2022) Obesity	29	23–58	Healthy	Lipedema	NIRF (ICG)	Leg	0.9 ± 0.4		

			Intervention						
Diseased			Type of intervention	Healthy			Diseased		
Frequency (contractions/min)	Pressure (mm Hg)	Velocity (cm/s)		Frequency (contractions/min)	Pressure (mm Hg)	Velocity (cm/s)	Frequency (contractions/min)	Pressure (mm Hg)	Velocity (cm/s)
	LE: 13.6 (7.8–17.5) No LE: 4.5 (0.5–9.2)		Flush and fill		86 CI ± 3.7 (Occlusion pressure)				
0.53 ± 0.39									
			Mechanical loading (60 mm Hg)			Median 0.6 (0.2–1.4) <sup>a</sup>			
			Hyperthermia	1.46 ± 0.5		1.83 ± 0.64			
			Exercise	0.68 ± 0.25		2.2 ± 0.63			
			10-min postexercise	0.35 ± 0.19		1.83 ± 0.64			
			Increased gravitational force	1.2 ± 0.5		1.7 ± 0.42			
			Handgrip exercise	0.9 ± 0.4		1.2 ± 0.3			
			Hyperthermia	1.5 ± 0.5		1.1 ± 0.4			
			Manual lymph drainage	Forearm: 1 <sup>a</sup> Elbow: 1.4 <sup>a</sup>		Forearm: 1.33 <sup>a</sup> Elbow: 1.19 <sup>a</sup>			
			Compression garment	Forearm: 1.2 <sup>a</sup> Elbow: 1.8 <sup>a</sup>		Forearm: 1.0 <sup>a</sup> Elbow: 1.14 <sup>a</sup>			
	24 ± 19	0.05 ± 0.15 <sup>a</sup>							
0.8 ± 0.1	50.8 ± 3.1	2.3 ± 0.3 <sup>a</sup>							
			Amlodipine	0.4 ± 0.2	53.9 ± 13.9	1.8 ± 1.0			
0.4 ± 0.3	54.8 ± 16.2	1.8 ± 0.8 <sup>a</sup>	Hyperthermia (5min)	1.4 ± 1.0		Unchanged	0.9 ± 0.5		0.5 ± 0.7
		0.008 ± 0.003 <sup>a</sup>							
Arm: 0.3 ± 0.3 Leg: 0.2 ± 0.2		Arm: 0.7 ± 1.0 Leg: 0.8 ± 0.4							
C2: 0.9 ± 0.2 C3: 1.1 ± 0.6 C4: 0.6 ± 0.4									
Lipedema Stage: Stage 1: 1.4 ± 0.6 Stage 2: 1.4 ± 0.7 Stage 3: 1.8 ± 0.1									

(Continues)

TABLE 1 (Continued)

In Vivo Summary									
Reference	N	Age, Years	Control group	Morbidity	Method	Limb	Baseline		
							Control/healthy		
							Frequency (contractions/min)	Pressure (mm Hg)	Velocity (cm/s)
Saito (2015) Lymphatic Research and Biology	465	30–85	NA	Healthy	NIRF (ICG)	Leg		30–39 years: 26.9 ± 16.2 40–49 years: 24.7 ± 15.5 50–59 years: 22.3 ± 15.1 60–69 years: 20.6 ± 14.6 70 years: 19.5 ± 14.4	
Tan (2011) Arch Phys Med Rehabil	22	18–68	Healthy and Own Control	LE	NIRF (ICG)	Arm and Leg			H-Arm: 0.7 ± 0.32 H-Leg: 0.94 ± 0.80 A-Arm: 0.68 ± 0.29 A-Leg: 0.71 ± 0.35
Telinius (2014) J Physiol	6	26 ± 0.4	Healthy (Placebo)	Healthy	NIRF (ICG)	Leg	0.77 ± 0.15	58 ± 3.8	1.2 ± 0.2 <sup>a</sup>
Unno (2010) J Vasc Surg	65	58.5 ± 13.5 71.9 ± 12.1	Healthy and AAA	LE	NIRF (ICG) & DynLS	Leg		Sitting NIRF: 29.3 ± 16.0 Supine NIRF: 25.2 ± 16.7 Supine DynLS: 26.4 ± 16.5	
Yamamoto (2014) Ann Plast Surg	15	41–74	Own control	Breast cancer w/ unilateral LE	NIRF (ICG)	Arm			0.5 ± 0.3 <sup>a</sup>

Note: () indicates range. Values listed as mean ± standard deviation unless otherwise indicated.

Abbreviations: AAA, abdominal aortic aneurism; A-Arm, asymptomatic arm; ADB, arm dermal backflow stage; A-Leg, asymptomatic leg; BCRL, breast cancer treatment-related lymphedema; C2-C4, clinical, etiological, anatomical, and pathophysiological (CEAP) classification system of venous insufficiency stage 2-4; CVI, chronic venous insufficiency; DynLS, dynamic lymphoscintigraphy; H-Arm, healthy arm; H-Leg, healthy leg; ICG, Indocyanine Green; ISL, International Society of Lymphology stage; LE, lymphedema; NIRF, near-infrared fluorescence imaging; OC-Arm, own control arm; OC-Leg, own control leg; SD, standard deviation.

<sup>a</sup>Converted from original values.

### 3 | RESULTS

The PubMed search returned 2885 results. Title and abstract screening excluded 2810 papers and of the remaining 73 papers, 21 were found eligible upon full-text screening. Screening of reference lists of included papers yielded an additional seven articles for inclusion. In total, 28 papers (Amann-Vesti et al., 2003; Belgrado et al., 2016; Bell et al., 2020; Gray et al., 2016; Groenlund et al., 2017; Holm-Weber et al., 2022; Kelly, Mohanakumar, Telinius,

et al., 2020; Lopera et al., 2017; Majgaard et al., 2022; Modi et al., 2007; Mohanakumar et al., 2018, 2019, 2020, 2021; Rane et al., 2013; Rasmussen et al., 2010, 2021, 2022; Saito et al., 2015; Tan et al., 2011; Telinius et al., 2010, 2015, 2017; Telinius, Baandrup, et al., 2014; Telinius, Kim, et al., 2014; Telinius, Mohanakumar, et al., 2014; Unno et al., 2010; Yamamoto et al., 2014) met the inclusion criteria, see Figure 1.

Of these, 20 were in vivo studies, seven were ex vivo and one study contained both in vivo and ex vivo data.

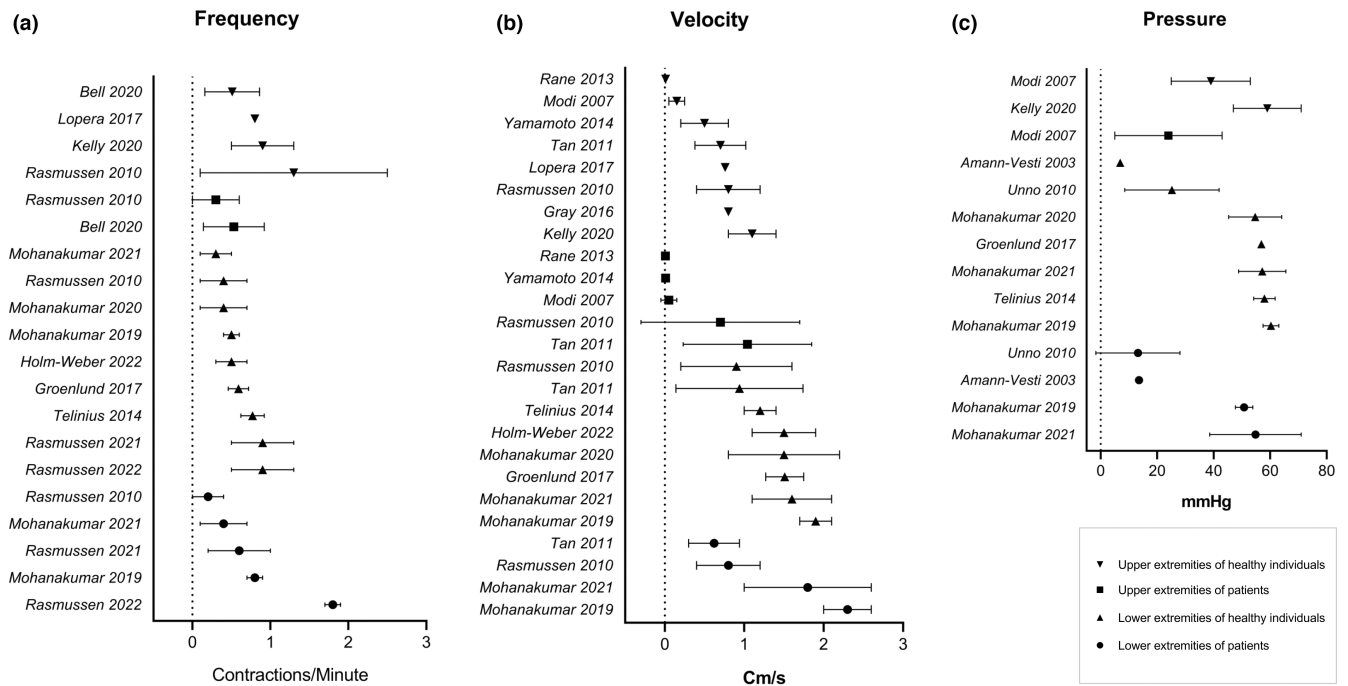
Intervention									
Diseased			Type of intervention	Healthy			Diseased		
Frequency (contractions/min)	Pressure (mm Hg)	Velocity (cm/s)		Frequency (contractions/min)	Pressure (mm Hg)	Velocity (cm/s)	Frequency (contractions/min)	Pressure (mm Hg)	Velocity (cm/s)
		Arm: 1.04±0.81 Leg: 0.62±0.32	Manual lymph drainage			H-Arm: 0.80±0.40 H-Leg: 1.27±1.11 A-Arm: 0.87±0.34 A-Leg: 0.76±0.59		Arm: 1.19±0.69 Leg: 0.95±0.66	
			Nifedipine	1.05±0.16	58±3.1	1.3±0.2 <sup>a</sup>			
Sitting NIRF: 13.2±14.9									
		ISL 0: 0.2±0.2 <sup>a</sup> ISL 1: 0.09±0.1 <sup>a</sup> ISL 2: 0.03±0.02 <sup>a</sup> ISL 3: 0.01±0.004 <sup>a</sup> ADB 1: 0.35±0.0 <sup>a</sup> ADB 2: 0.13±0.11 <sup>a</sup> ADB 3: 0.04±0.01 <sup>a</sup> ADB 4: 0.01±0.005 <sup>a</sup> ADB 5: 0.008±0.002 <sup>a</sup>							

Studies were published between 2003 and 2022, with the majority from 2010 and up. The method most often used to investigate the lymphatic parameters in vivo was near-infrared fluorescence imaging (NIRF) using indocyanine green (ICG) as the contrast agent (86%). The participants examined included both healthy people and patients with a Fontan circulation, lymphedema, breast cancer, Fabry's disease, venous insufficiency, lipedema, and rheumatoid arthritis. In vivo study characteristics and lymphatic functional parameters are summarized in [Table 1](#).

### 3.1 | In vivo results

#### 3.1.1 | Baseline functional properties of peripheral lymphatic vessels in healthy individuals

The contraction frequency of relaxed lymphatic vessels from healthy participants ranged from 0.5 to 1.3/min in the upper extremities and 0.3 to 0.9 min<sup>-1</sup> in the lower extremities ([Figure 2a](#)).



**FIGURE 2** Plot of baseline values of lymphatic vessel (a) contraction frequency; (b) velocity of lymphatic fluid; (c) lymphatic pressure in the upper and lower extremities from both healthy participants and patients. Values reported as mean  $\pm$  SD where available.

Lymphatic pressure was between  $39 \pm 14$  and  $59 \pm 12$  mm Hg in the upper extremities and between 6.9 and  $60.3 \pm 2.8$  mm Hg in the lower extremities (Figure 2b). The lower measurement of 6.9 (range 1.5 to 13) mm Hg was assessed using lymphatic capillary puncture as the only study utilizing this method (Amann-Vesti et al., 2003). If limiting to only including NIRF imaging, the pressure range in the lower extremities was between  $19.5 \pm 14.4$  and  $60.3 \pm 2.8$  mm Hg.

Finally, the velocity of lymphatic movement in the upper extremities ranged from  $0.01 \pm 0.002$  to  $1.1 \pm 0.3$  cm/s (Figure 2c). The lower limit was measured using spin labeling magnetic resonance imaging method as the only study (Rane et al., 2013). If using NIRF imaging only, the range was 0.76 to  $1.1 \pm 0.3$  cm/s. In the lower extremities this range was  $0.9 \pm 0.7$  to  $1.9 \pm 0.2$  cm/s.

Generally, the velocity appeared slightly higher in the lower extremities compared with the upper, and the contraction frequency was the opposite—slightly lower in the lower extremities. The lymphatic pressure did not seem to differ much between extremities.

### 3.1.2 | Baseline functional properties of peripheral lymphatic vessels in patients

Contraction frequency did not differ significantly with disease except one study which found lower frequencies in the upper and lower extremities affected by lymphedema

(Rasmussen et al., 2010) and another study which on the contrary found an increase in contraction frequency of lower extremities affected by lipedema (Rasmussen et al., 2022) (Figure 2a).

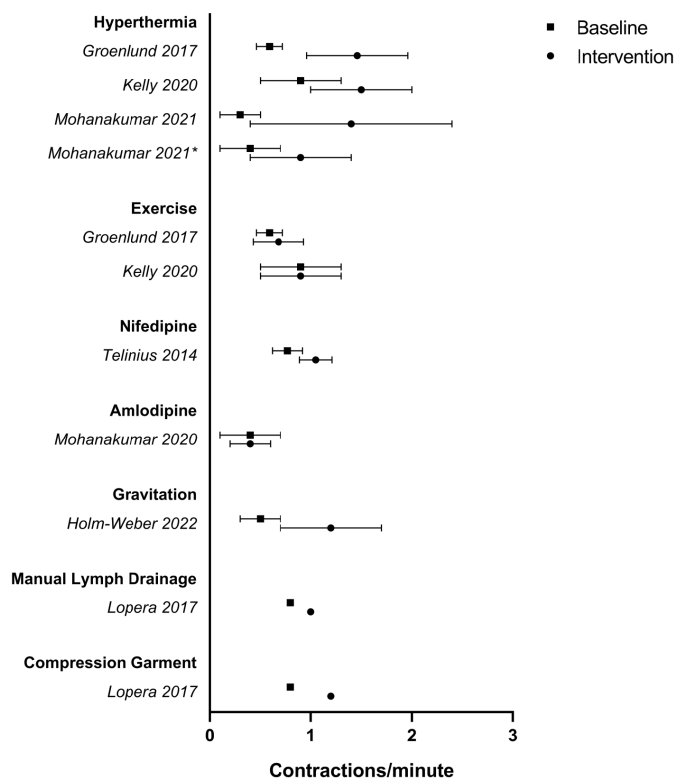
Pressure in investigated lower extremities of Fontan patients and upper extremities of breast cancer-related lymphedema was generally lower compared to healthy controls (Modi et al., 2007; Mohanakumar et al., 2019, 2021). One study did, however, find a higher pressure in the legs of Fabry patients with lymphedema (Amann-Vesti et al., 2003) (Figure 2b).

The lymph velocity was generally lower in the upper extremities affected by lymphedema except in one study which showed an increase (Tan et al., 2011) (Figure 2c). One study demonstrated a linear relationship between lower velocity and progressing disease stage (Yamamoto et al., 2014). Velocity in the lower extremities remained either unchanged, increased or decreased in various diseases, and thus no clear, unifying tendency was found.

### 3.1.3 | Effect of interventions

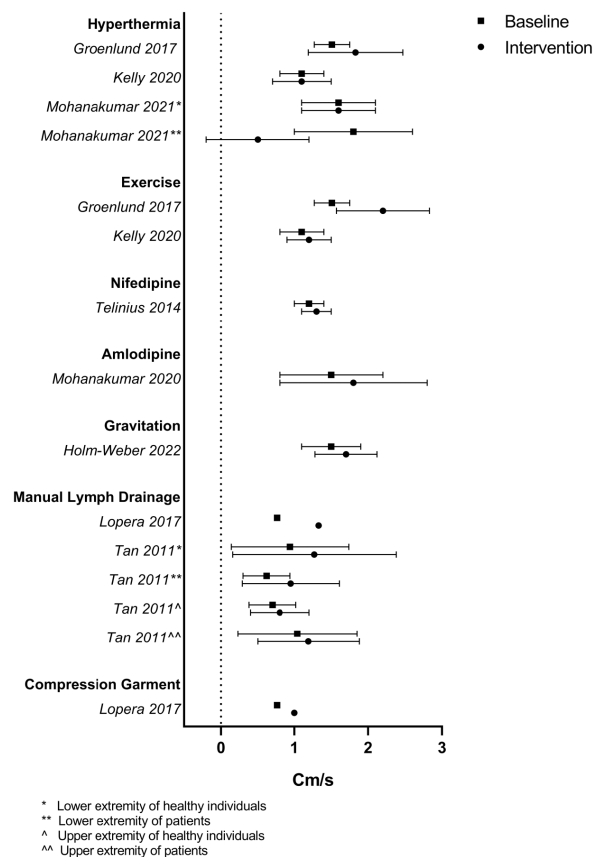
Exposure of limbs to various stimuli resulted in changes in contractile function. Hyperthermia, exposure to increased gravitational forces, and treatment with nifedipine all caused an increase in contraction frequency. This was not the case for pressure or velocity, where a

## (a) Effect of Interventions on Contraction Frequency



\* In Fontan patients

## (b) Effect of Interventions on Velocity



\* Lower extremity of healthy individuals  
 \*\* Lower extremity of patients  
 ^ Upper extremity of healthy individuals  
 ^^ Upper extremity of patients

**FIGURE 3** Plot of baseline and postintervention values of (a) contraction frequency and (b) velocity. All values reported as mean and where available  $\pm$  SD.

tendency toward an increase is noted, but some studies also found unchanged values (Figure 3).

### 3.2 | Ex vivo results

All ex vivo studies were carried out in lymphatic vessels obtained from diseased patients. Two types of vessels have been examined: the thoracic duct (TD) and mesenteric lymphatic vessels (MLV). All studies reported here utilized a wire myograph setup for examinations. Contraction frequencies preactivation ranged between  $2.1 \pm 0.7$  and  $5.5 \pm 1.2 \text{ min}^{-1}$  in MLVs and  $1.2 \pm 0.1$  and  $4.3 \pm 0.4 \text{ min}^{-1}$  in TDs. Noticeably, some vessels only exhibited spontaneous contractions after physical stimulation (occurring during the exchange of physiological solution in myograph) or upon vasoconstriction with agonists and subsequent wash-out. These postactivation contraction frequencies were within the same range as preactivation (or spontaneous) frequencies, except for ivabradine which revealed a markedly higher postactivation frequency. Ex vivo parameters are summarized in Table 2.

Several pharmacologic agents have been examined with the lymphatic vessels showing reactivity when exposed to drugs that directly and indirectly affect cation and anion channels of vascular smooth muscle cells, adrenoceptors, and changes in length–diameter relationship (stretching of the lymphatic vessel).

Generally, lymphatic vessel reactivity to known vasoconstrictors and dilators corresponds well to what is described in the blood vascular system. That is, vasoconstrictors such as norepinephrine and endothelin-1 induced increased contraction frequencies and tone in the lymphatic vessels, while vasodilators such as bradykinin and acetylcholine typically induced relaxation.  $\text{Ca}^{2+}$ ,  $\text{Na}^{+}$ , and  $\text{Cl}^{-}$  channel antagonists along with  $\text{K}^{+}$  channel agonists all decrease or complete stop of contractions, while  $\text{K}^{+}$  channel antagonists and  $\text{Na}^{+}$  agonist increase contraction frequency.

Despite evidence of HCN/funny channels existing in lymphatic vessels, exposure to HCN/funny channel antagonists, known to lower frequency in cardiac pacemaker cells, increased contraction frequency in the lymphatic vessels. This positive chronotropic effect was only evident

TABLE 2 Summary of ex vivo functional properties.

Ex vivo summary							
Reference	N <sup>a</sup>	Age, Years	Type of vessel	Avg. diameter <sup>b</sup> (mean ± SD)	Morbidity	Baseline  Frequency <sup>c</sup> (contractions/ minute)	Baseline tension (Nm <sup>-1</sup> )
Majgaard (2022) Physiological Reports	66	Range 40–84	TD MLV	1675 ± 97 µm (±SEM) 346 ± 36 µm (±SEM)	Esophageal and cardia cancer GBP	4.3 ± 0.4 4.4 ± 0.5	
Mohanakumar (2018) Am J Physiol Heart Circ Physiol	42	64.8 ± 1.6 (±SEM) 64.8 ± 1.6 (±SEM)	TD MLV	1.47 mm 340 µm	Esophageal and cardia cancer GBP/IPAA	2.9 ± 0.6 5.5 ± 1.2	
Telinius (2010) Am J Physiol Heart Circ Physiol	26	64 ± 12 (±SD)	TD	2,21 (95% CI 1.1–3.35)	Esophageal and cardia cancer		
Telinius (2014) J Physiol	65	Range 33–85	TD MLV	≈2 mm ≈300 µm	Esophageal and cardia cancer GBP	1.2 ± 0.1 2–3/min	
Telinius (2014) Am J Physiol Heart Circ Physiol	54	65 ± 1 (±SEM)	TD MLV	Not stated Not stated	Esophageal and cardia cancer GBP	2.2 ± 0.3 2.1 ± 0.7	0.56 ± 0.16
Telinius (2014) Am J Physiol Heart Circ Physiol	35	63 ± 10 (±SD)	TD		Esophageal and cardia cancer		
Telinius (2015) J Physiol	62	Range 30–82	TD MLV	Not stated Not stated	Esophageal and cardia cancer GBP		
Telinius (2017) Lymphatic Research and Biology	44	Range 19–69	TD MLV MLV	Not stated Not stated Not stated	Esophageal and cardia cancer GBP IPAA	3.4 ± 1.7 Range ≈1–6/min	

Abbreviations: 4-AP, 4-aminopridine; ACh, acetylcholine; CCRC, cumulative concentration-response curve; CPA, cyclopiazonic acid; ET-1, endothelin-1; GBP, gastric bypass; IPAA, ileal pouch-anal anastomosis; L-NAME, *N*<sup>G</sup>-nitro-L-arginine methyl ester; MCh, metacholine; MLV, mesenteric lymphatic vessel; NE, norepinephrine; NPPB, 5-nitro-2-(3-phenylpropylamino) acid; NPY, neuropeptide Y; SD, standard deviation; SP, substance P; TD, thoracic duct; TEA, tetraethylammonium; TTX, tetrodotoxin.

<sup>a</sup>Number of patients is how the *N* values are defined in all papers (the number of segments can be much higher in each experiment, but the patient average is reported if there has been a repeated experiment).

<sup>b</sup>Diameter, as derived from the internal circumference in the passive length-tension normalization (at 21 mm Hg for TD and 22 mm Hg for MLV).

<sup>c</sup>Frequency, either spont (after normalization but before application of noradrenaline) or with- or after-stimulation (has been given small amount of noradrenaline, or has become “spontaneous” after exposure to agonist and washout).

Intervention			Frequency change (contractions/minute)	Passive tension (Nm-1)	Avg. active tension (Nm-1)
Type of intervention	Concentration	Overall effect of intervention			
Ivabradine	$\geq 10 \mu\text{M}$	Contraction	↑		
ZD7288	$\geq 30 \mu\text{M}$	Contraction	↑		
Cesium	5 mM	No change	↑		
Pyrilamine	10 $\mu\text{M}$	No effect	–		
Histamine	0.1 pM—10 $\mu\text{M}$	No effect	–		
Extracellular $\text{Cl}^-$ substitution	200 $\mu\text{M}$	Inhibition of NE contraction	↓/stop		
NE CCRC ( $\text{Cl}^-$ subst)	20 $\mu\text{M}$	Inhibition of NE contraction	↓/stop		
DIDS	10 nM—100 $\mu\text{M}$	No change to NE contraction	↓/stop		
Furosemide	10 $\mu\text{M}$	Inhibition of NE contraction	↓/stop		
DIDS + Furosemide		Inhibition of spontaneous contraction	↓/stop		
NPPB		Contraction	↑		
CPA					
Length-tension	1 nM—10 $\mu\text{M}$	Contraction	↑	$3.11 \pm 0.67$	$6.24 \pm 0.75$
NE	1 pM—0.1 $\mu\text{M}$	Contraction	↑		(max L-T)
ET-1	1 pM—0.1 $\mu\text{M}$	Contraction	↑		$2.59 \pm 0.36$
U46619	10 $\mu\text{M}$	Relaxation (of precontracted)	↓		$5.31 \pm 1.3$
ACh	1 $\mu\text{M}$	Relaxation (of precontracted)	↓		$5.62 \pm 1.2$
Bradykinin	100 $\mu\text{M}$	Contraction	↑		
L-NAME	100 $\mu\text{M}$ + 1 $\mu\text{M}$	Contraction	↑		
L-NAME + indomethacin					
Nifedipine	0.1 nM—1 $\mu\text{M}$	Inhibition of phasic activity	↓		
Verapamil	0.1 nM—3 $\mu\text{M}$	Inhibition of phasic activity	↓		
NE + Nifedipine	10 nM—10 $\mu\text{M}$ /20 nM	Reduction of maximum response to NE	–		
TEA	1 mM	Contraction	↑	$0.31 \pm 0.1$	
Barium	30 $\mu\text{M}$	Contraction	↑		
Paxilline	40 $\mu\text{M}$ + 1 mM	No change in tone	↑		
Apamin	10 mM	No effect	–		
TRAM-34		No effect	–		
Apamin + TRAM-34		No effect	–		
NS309		No effect	–		
4-AP		Tansient increase (few mins)	↑ (transient)		
Glibenclamide			↑		
Pinacidil			↓/stop		
K extracellular			↑		
Cromakalim			↓/stop		
NE	10 $\mu\text{M}$	Contraction (variable)	(Apparent increase in freq)		
NPY	1 $\mu\text{M}$	Contraction (variable)			
SP	10 $\mu\text{M}$	Contraction (variable)	↑		
Acetylcholine or MCh	10 $\mu\text{M}$	Contraction (variable)			
ACh (or MCh) + atropine	10 $\mu\text{M}$	No contraction			
Tyramine	2—20 Hz	Contraction			
Electric field stimulation		Contraction			
TTX		Inhibition of phasic activity	↓/stop	Gain of tone in both TD and MLV	
Veratridine		Contraction	↑		
SP (TD)	0.1 nM—10 $\mu\text{M}$	Little or no effect	Not analysed	$0.64 \pm 0.46$	$0.93 \pm 0.45$
SP (MLV; GBP)	0.1 nM—10 $\mu\text{M}$	Vasorelaxation (lower BL tone)	Not analysed	$0.47 \pm 0.24$	$0.78 \pm 0.4$
NE (MLV; IPAA)	1 nM—10 $\mu\text{M}$	Contraction	↑		

at supraoptimal concentrations, and unlikely a direct effect via HCN channels.

## 4 | DISCUSSION

This systematic review identified 28 papers about human lymphatic vascular functional properties *in vivo* and *ex vivo* over a span of 22 years.

The overall impression is that of a dynamic system with the ability to adapt to various stimuli and demands. This adaptation can occur within minutes as shown in the cases of physical stress with hyperthermia, manual compression, and changes in gravitational influence. All stimuli investigated induced either an increase or unchanged lymphatic frequency and velocity in healthy arms and legs *in vivo*.

While correlating greater frequency to greater flow seems appealing, it is important to remember that contraction force also plays a significant role—similar to stroke volume in cardiac output (Vincent, 2008). *In vivo* lymphatic contraction force is often approximated by pumping pressure, but with the current methods this only takes into account the superficial vessel pressures. The actual amount of fluid moved in the limb is challenging to determine, due to both the small volume and acellular nature of lymph fluid, which makes noninvasive techniques such as ultrasound suboptimal. Thus, a higher frequency does not necessarily equal a higher flow or more “effective” lymphatic function. To prove or dismiss that assumption, studies that examine the *in vivo* relationship between the various parameters as well as considering the whole lymphatic system are needed.

Results from *ex vivo* studies are not directly translatable to *in vivo* effects, as demonstrated in the study by Telinius, Mohanakumar, et al. (2014). Here, the calcium channel blocker nifedipine decreased contraction frequency *ex vivo* whereas *in vivo* testing resulted in an increase in frequency. The mechanism behind this difference is unclear, but the *ex vivo* study focused on central lymphatic vessels such as the mesenteric and thoracic duct, whereas the *in vivo* study targeted the peripheral vessels. There could be differences in channels and receptors in the central versus peripheral lymphatic vessels. Testing this would require the donation of peripheral tissue and techniques to dissect and mount these.

Aside from characterizing basic lymphatic physiology, many studies have tended to focus on ways to stimulate and increase lymphatic function. This emphasizes the need for treatment options for the dysfunctional lymphatic circulation as seen in lymphedema, or recently as proposed and described in an animal heart failure model (Abraham et al., 2021). Another example

is the inhibitory effects of acidosis on lymphatic contraction frequency (Moeller et al., 2019), making the lymphatic system a potential target in the treatment of acidosis-associated edema. However, it is also worth highlighting some of the potential advantages that come with lowering the movement of lymphatic fluid. This could be applicable in, for example, snakebite patients where the lymphatic system plays a key transport role. Animal studies of snake bites have suggested a significant delay in time to mortality after topical application of nifedipine (van Helden et al., 2014). This topical administration route has not been tested in humans, but it does correspond well with the *ex vivo* findings from Telinius, Mohanakumar, et al. (2014).

The relatively small inclusion number in this review does not reflect lack of studies investigating the lymphatic vascular system *per se*, but most of these studies utilize methods that examine the morphological features of the lymphatics rather than functional (Munn & Padera, 2014; Polomska & Proulx, 2021). While this underlines the novelty of this new field—as well as the opportunities—it is also a work in progress, and with that comes a number of limitations related to especially study design and methods. Here we list some of the most obvious and important limitations encountered.

First, there is a general issue with a small sample size reducing the power of the studies comparing groups of patients or measuring the effect of an intervention. One study (Saito et al., 2015) did include a larger study population of 465 participants and was able to show an inverse relationship between age and lymphatic pressure. Others present data including few participants in each group, the smallest study including only six participants in total.

Secondly, the investigative and analytical methods are characterized by subjective interpretation, resulting in uncertainty of measurements and low external validity of each study. This is also evident in some of the relatively large SDs reported. Some studies have tried to address the analytical variation by doing multiple, independent analyses for each data set. These studies report high intraclass correlation coefficients as an expression of low interobserver variation. The parameter displaying the highest variation was the velocity measurements (Kelly, Mohanakumar, Telinius, et al., 2020). This could be an argument for creating more standardized methods for assessing this parameter in particular.

Finally, comparing studies utilizing different investigative methods poses great difficulties. The results change dramatically when the lymphatic function is studied by lymphatic capillary puncture or spin label measurement compared to NIRF investigations. Most of the identified studies use the NIRF method for investigation, and although their measurements appear to be somewhat consistent, it is unclear

whether this is due to the method's superiority or simply its widespread adoption. It is also relevant to consider the lack of investigations of the deeper lymphatic system in these studies. The NIRF imaging system has a maximum depth range of 1–2 cm, thus the estimation of the overall function and transport capacity of the lymphatic system as a whole cannot be assessed using these techniques. Interestingly, the one study utilizing spin labeling MRI to visualize deeper lymphatic vessels (Rane et al., 2013) found dramatically lower flow velocities in both healthy and lymphedema-affected upper extremities compared to NIRF and lymphoscintigraphy results. Perhaps a sign that deeper lymphatic vessels operate differently than the superficial. However, a literature search yielded no other studies using the same spin label technique, making it difficult to exclude the possibility of it simply being a case of conflicting methods. One other study using another MRI technique (contrast-enhanced) was identified (Borri et al., 2015). It included three patients and displayed a velocity of 0.035 cm/s in the upper extremities affected by breast cancer-related lymphedema and 0.16 cm/s in the ipsilateral, nonaffected arm. Thus, a higher velocity than measured using spin labeling MRI (0.008 to 0.01 cm/s) but still drastically lower compared to the NIRF investigations. In conclusion, these two MRI studies measuring the function of deeper lymphatic vessels indicate lower velocity scores compared to superficial vessels, but it is hard to make a direct comparison due to different methods and a very small sample size (six and three participants).

## 5 | CONCLUSION

Despite the potential benefits of a more profound knowledge about lymphatic transport function, interest in this area still seems modest. Both in vivo and ex vivo human studies gives the impression of a vascular system that is highly adaptable to physiological as well as pharmacological stimuli. This creates potential for new target areas in the treatment of lymph-related diseases ranging from heart failure to neglected tropical diseases such as snakebite envenoming. So far, investigations of lymphatic transport function have shown promising results, but there is still a long way to go before applying it in a clinical context. It is clear, that more systematic approaches are needed if we are to fully understand this underappreciated and complex vascular system and eventually be able to treat patients with new lymphatic-specific treatments.

## FUNDING INFORMATION

During the writing of this review, authors LT and VH were partly funded by Bent Thorberg's Foundation (private foundation) and a common grant from The Novo Nordisk Foundation (grant #NFF17SA0030576), respectively.

## ETHICS STATEMENT

This review is not subject to ethical approval, as only previously published data is reported.

## CONFLICT OF INTEREST STATEMENT

The authors declare no financial conflicts of interest.

## ORCID

Lene Thorup  <https://orcid.org/0000-0002-5208-8353>

Vibeke Hjortdal  <https://orcid.org/0000-0002-8047-0015>

## REFERENCES

- Abraham, W. T., Jonas, M., Dongaonkar, R. M., Geist, B., Ueyama, Y., Render, K., Youngblood, B., Muir, W., Hamlin, R., & del Rio, C. L. (2021). Direct interstitial decongestion in an animal model of acute-on-chronic ischemic heart failure. *Journal of the American College of Cardiology Basic to Translation Science*, 6, 872–881.
- Adamczyk, L. A., Gordon, K., Kholová, I., Meijer-Jorna, L. B., Telinius, N., Gallagher, P. J., van der Wal, A. C., & Baandrup, U. (2016). Lymph vessels: The forgotten second circulation in health and disease. *Virchows Archiv*, 469, 3–17.
- Alitalo, K. (2011). The lymphatic vasculature in disease. *Nature Medicine*, 17, 1371–1380.
- Amann-Vesti, B. R., Gitzelmann, G., Widmer, U., Bosshard, N. U., Steinmann, B., & Koppensteiner, R. (2003). Severe lymphatic microangiopathy in Fabry disease. *Lymphatic Research and Biology*, 1, 185–189.
- Belgrado, J. P., Vandermeeren, L., Vankerckhove, S., Valsamis, J. B., Malloizel-Delaunay, J., Moraine, J. J., & Liebens, F. (2016). Near-infrared fluorescence lymphatic imaging to reconsider occlusion pressure of superficial lymphatic collectors in upper extremities of healthy volunteers. *Lymphatic Research and Biology*, 14, 70–77.
- Bell, R. D., Rahimi, H., Kenney, H. M., Lieberman, A. A., Wood, R. W., Schwarz, E. M., & Ritchlin, C. T. (2020). Altered lymphatic vessel anatomy and markedly diminished lymph clearance in affected hands of patients with active rheumatoid arthritis. *Arthritis & Rheumatology*, 72, 1447–1455.
- Borri, M., Schmidt, M. A., Gordon, K. D., Wallace, T. A., Hughes, J. C., Scurr, E. D., Koh, D. M., Leach, M. O., & Mortimer, P. S. (2015). Quantitative contrast-enhanced magnetic resonance lymphangiography of the upper limbs in breast cancer related lymphedema: An exploratory study. *Lymphatic Research and Biology*, 13, 100–106.
- Breslin, J. W., Yang, Y., Scallan, J. P., Sweat, R. S., Adderley, S. P., & Murfee, W. L. (2018). Lymphatic vessel network structure and physiology. *Comprehensive Physiology*, 9, 207–299.
- Briggs Boedtkjer, D., Rumessen, J., Baandrup, U., Skov Mikkelsen, M., Telinius, N., Pilegaard, H., Aalkjaer, C., & Hjortdal, V. (2013). Identification of interstitial Cajal-like cells in the human thoracic duct. *Cells, Tissues, Organs*, 197, 145–158.
- Brotons, M. L., Bolca, C., Frechette, E., & Deslauriers, J. (2012). Anatomy and physiology of the thoracic lymphatic system. *Thoracic Surgery Clinics*, 22, 139–153.
- Cifarelli, V., & Eichmann, A. (2019). The intestinal lymphatic system: Functions and metabolic implications. *Cellular and Molecular Gastroenterology and Hepatology*, 7, 503–513.
- Covidence systematic review software. (2022). *Veritas health innovation*. Veritas Health Innovation. [www.covidence.org](https://www.covidence.org)

- Gray, R. J., Worsley, P. R., Voegeli, D., & Bader, D. L. (2016). Monitoring contractile dermal lymphatic activity following uniaxial mechanical loading. *Medical Engineering & Physics*, 38, 895–903.
- Groenlund, J. H., Telinius, N., Skov, S. N., & Hjortdal, V. (2017). A validation study of near-infrared fluorescence imaging of lymphatic vessels in humans. *Lymphatic Research and Biology*, 15, 227–234.
- Hokkanen, K., Tirronen, A., & Yla-Herttuala, S. (2019). Intestinal lymphatic vessels and their role in chylomicron absorption and lipid homeostasis. *Current Opinion in Lipidology*, 30, 370–376.
- Holm-Weber, T., Kristensen, R. E., Mohanakumar, S., & Hjortdal, V. E. (2022). Gravity and lymphodynamics. *Physiological Reports*, 10, e15289.
- Kelly, B., Mohanakumar, S., & Hjortdal, V. E. (2020). Diagnosis and Management of Lymphatic Disorders in congenital heart disease. *Current Cardiology Reports*, 22, 164.
- Kelly, B., Mohanakumar, S., Telinius, N., Alstrup, M., & Hjortdal, V. (2020). Function of upper extremity human lymphatics assessed by near-infrared fluorescence imaging. *Lymphatic Research and Biology*, 18, 226–231.
- Levick, J. R. (2004). Revision of the starling principle: New views of tissue fluid balance. *The Journal of Physiology*, 557, 704.
- Lopera, C., Worsley, P. R., Bader, D. L., & Fenlon, D. (2017). Investigating the short-term effects of manual lymphatic drainage and compression garment therapies on lymphatic function using near-infrared imaging. *Lymphatic Research and Biology*, 15, 235–240.
- Majgaard, J., Skov, F. G., Kim, S., Hjortdal, V. E., & Boedtker, D. M. B. (2022). Positive chronotropic action of HCN channel antagonism in human collecting lymphatic vessels. *Physiological Reports*, 10, e15401.
- Michel, C. C., Woodcock, T. E., & Curry, F. R. E. (2020). Understanding and extending the Starling principle. *Acta Anaesthesiologica Scandinavica*, 64, 1032–1037.
- Modi, S., Stanton, A. W. B., Svensson, W. E., Peters, A. M., Mortimer, P. S., & Levick, J. R. (2007). Human lymphatic pumping measured in healthy and lymphoedematous arms by lymphatic congestion lymphoscintigraphy. *The Journal of Physiology*, 583, 271–285.
- Moeller, A. L., Hjortdal, V. E., Boedtker, D. M. B., & Boedtker, E. (2019). Acidosis inhibits rhythmic contractions of human thoracic ducts. *Physiological Reports*, 7, 1–17.
- Mohanakumar, S., Kelly, B., Turquette, A. L. R., Alstrup, M., Amato, L. P., Barnabe, M. S. R., Silveira, J. B. D., Amaral, F., Manso, P. H., Jatene, M. B., & Hjortdal, V. E. (2021). Functional lymphatic reserve capacity is depressed in patients with a Fontan circulation. *Physiological Reports*, 9, e14862.
- Mohanakumar, S., Majgaard, J., Telinius, N., Katballe, N., Pahle, E., Hjortdal, V., & Boedtker, D. (2018). Spontaneous and alpha-adrenoceptor-induced contractility in human collecting lymphatic vessels require chloride. *American Journal of Physiology. Heart and Circulatory Physiology*, 315, H389–H401.
- Mohanakumar, S., Telinius, N., Kelly, B., & Hjortdal, V. (2020). Reduced lymphatic function predisposes to Calcium Channel blocker edema: A randomized placebo-controlled clinical trial. *Lymphatic Research and Biology*, 18, 156–165.
- Mohanakumar, S., Telinius, N., Kelly, B., Lauridsen, H., Boedtker, D., Pedersen, M., de Leval, M., & Hjortdal, V. (2019). Morphology and function of the lymphatic vasculature in patients with a Fontan circulation. *Circulation. Cardiovascular Imaging*, 12, e008074.
- Munn, L. L., & Padera, T. P. (2014). Imaging the lymphatic system. *Microvascular Research*, 96, 55–63. <https://doi.org/10.1016/j.mvr.2014.06.006>
- Oliver, G., & Alitalo, K. (2005). The lymphatic vasculature: Recent progress and paradigms. *Annual Review of Cell and Developmental Biology*, 21, 457–483.
- Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., ... Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, 372, n71.
- Polomska, A. K., & Proulx, S. T. (2021). Imaging technology of the lymphatic system. *Advanced Drug Delivery Reviews*, 170, 294–311.
- Rane, S., Donahue, P. M. C., Towse, T., Ridner, S., Chappell, M., Jordi, J., Gore, J., & Donahue, M. J. (2013). Clinical feasibility of noninvasive visualization of lymphatic flow with principles of spin labeling MR imaging: Implications for lymphedema assessment. *Radiology*, 269, 893–902.
- Rasmussen, J. C., Aldrich, M. B., Fife, C. E., Herbst, K. L., & Sevick-Muraca, E. M. (2022). Lymphatic function and anatomy in early stages of lipedema. *Obesity (Silver Spring)*, 30, 1391–1400.
- Rasmussen, J. C., Tan, I. C., Marshall, M. V., Adams, K. E., Kwon, S., Fife, C. E., Maus, E. A., Smith, L. A., Covington, K. R., & Sevick-Muraca, E. M. (2010). Human lymphatic architecture and dynamic transport imaged using near-infrared fluorescence. *Translational Oncology*, 3, 362–372.
- Rasmussen, J. C., Zhu, B., Morrow, J. R., Aldrich, M. B., Sahihi, A., Harlin, S. A., Fife, C. E., O'Donnell, T. F., Jr., & Sevick-Muraca, E. M. (2021). Degradation of lymphatic anatomy and function in early venous insufficiency. *Journal of Vascular Surgery. Venous and Lymphatic Disorders*, 9, 720–730 e2.
- Saito, T., Unno, N., Yamamoto, N., Inuzuka, K., Tanaka, H., Sano, M., Sugisawa, R., Katahashi, K., & Konno, H. (2015). Low lymphatic pumping pressure in the legs is associated with leg edema and lower quality of life in healthy volunteers. *Lymphatic Research and Biology*, 13, 154–159.
- Scallan, J. P., Zawieja, S. D., Castorena-Gonzalez, J. A., & Davis, M. J. (2016). Lymphatic pumping: Mechanics, mechanisms and malfunction. *The Journal of Physiology*, 594, 5749–5768.
- Suy, R., Thomis, S., & Fourneau, I. (2016). The discovery of lymphatic system in the seventeenth century. Part I: The early history. *Acta Chirurgica Belgica*, 116, 260–266.
- Tan, I. C., Maus, E. A., Rasmussen, J. C., Marshall, M. V., Adams, K. E., Fife, C. E., Smith, L. A., Chan, W., & Sevick-Muraca, E. M. (2011). Assessment of lymphatic contractile function after manual lymphatic drainage using near-infrared fluorescence imaging. *Archives of Physical Medicine and Rehabilitation*, 92, 756–764 e1.
- Telinus, N., Baandrup, U., Rumessen, J., Pilegaard, H., Hjortdal, V., Aalkjaer, C., & Boedtker, D. B. (2014). The human thoracic duct is functionally innervated by adrenergic nerves. *American Journal of Physiology. Heart and Circulatory Physiology*, 306, 206–213.

- Telinius, N., Drewsen, N., Pilegaard, H., Kold-Petersen, H., de Leval, M., Aalkjaer, C., Hjortdal, V., & Boedtkjer, D. B. (2010). Human thoracic duct in vitro: Diameter-tension properties, spontaneous and evoked contractile activity. *American Journal of Physiology. Heart and Circulatory Physiology*, 299, H811–H818.
- Telinius, N., & Hjortdal, V. E. (2019). Role of the lymphatic vasculature in cardiovascular medicine. *Heart*, 105, 1777–1784.
- Telinius, N., Kim, S., Pilegaard, H., Pahle, E., Nielsen, J., Hjortdal, V., Aalkjaer, C., & Boedtkjer, D. B. (2014). The contribution of K(+) channels to human thoracic duct contractility. *American Journal of Physiology. Heart and Circulatory Physiology*, 307, H33–H43.
- Telinius, N., Majgaard, J., Kim, S., Katballe, N., Pahle, E., Nielsen, J., Hjortdal, V., Aalkjaer, C., & Boedtkjer, D. B. (2015). Voltage-gated sodium channels contribute to action potentials and spontaneous contractility in isolated human lymphatic vessels. *The Journal of Physiology*, 593, 3109–3122.
- Telinius, N., Majgaard, J., Mohanakumar, S., Pahle, E., Nielsen, J., Hjortdal, V., Aalkjaer, C., & Boedtkjer, D. B. (2017). Spontaneous and evoked contractility of human intestinal lymphatic vessels. *Lymphatic Research and Biology*, 15, 17–22.
- Telinius, N., Mohanakumar, S., Majgaard, J., Kim, S., Pilegaard, H., Pahle, E., Nielsen, J., de Leval, M., Aalkjaer, C., Hjortdal, V., & Boedtkjer, D. B. (2014). Human lymphatic vessel contractile activity is inhibited in vitro but not in vivo by the calcium channel blocker nifedipine. *The Journal of Physiology*, 592, 4697–4714.
- Unno, N., Nishiyama, M., Suzuki, M., Tanaka, H., Yamamoto, N., Sagara, D., Mano, Y., & Konno, H. (2010). A novel method of measuring human lymphatic pumping using indocyanine green fluorescence lymphography. *Journal of Vascular Surgery*, 52, 946–952.
- van Helden, D. F., Thomas, P. A., Dosen, P. J., Imtiaz, M. S., Laver, D. R., & Isbister, G. K. (2014). Pharmacological approaches that slow lymphatic flow as a snakebite first aid. *PLoS Neglected Tropical Diseases*, 8, 1–7.
- Vincent, J. L. (2008). Understanding cardiac output. *Critical Care*, 12, 12–14.
- Woodcock, T. E., & Michel, C. C. (2021). Advances in the Starling principle and microvascular fluid exchange; consequences and implications for fluid therapy. *Frontiers Veterinary Science*, 8, 1–11.
- Yamamoto, T., Narushima, M., Yoshimatsu, H., Yamamoto, N., Kikuchi, K., Todokoro, T., Iida, T., & Koshima, I. (2014). Dynamic indocyanine green (ICG) lymphography for breast cancer-related arm lymphedema. *Annals of Plastic Surgery*, 73, 706–709.

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Thorup, L., Hjortdal, A., Boedtkjer, D. B., Thomsen, M. B., & Hjortdal, V. (2023). The transport function of the human lymphatic system—A systematic review. *Physiological Reports*, 11, e15697. <https://doi.org/10.14814/phy2.15697>